

Attachment 5-10 Interim Guidelines for NIH Intramural Principal Investigators and for NIH Institutional Review Boards on Reporting Adverse Events

INTRODUCTION

In fulfilling its responsibility to protect the rights and welfare of human research subjects, an Institutional Review Board (IRB) reviews, approves and provides continuing oversight of research involving human subjects. An important part of this responsibility is the IRB's evaluation of events in which research subjects have been unexpectedly harmed or exposed to unanticipated risk. By regulation, both the Department of Health and Human Services and the Food and Drug Administration [HHS 45 CFR 46.103, FDA 21 CFR 56.108(b)] require that institutions that conduct or sponsor human subject research have written procedures for ensuring the prompt reporting to the IRB and others any unanticipated problems involving risks to subjects. At the NIH, these procedures are found in the NIH Multiple Project Assurance (MPA) and require written reports to the IRB and other NIH offices of unanticipated problems involving risks to subjects and others, or unexpected serious harm to subjects.

Assessing safety and efficacy of particular interventions is central to the design and implementation of clinical studies. Safety is mostly determined from data on frequency of adverse events. **Adverse events** are defined by the FDA as *any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or, if present at baseline, appears to worsen*. **Serious adverse events** are defined by the FDA as *any untoward medical occurrences that: (1) result in death, (2) are life threatening, (3) require (or prolong) hospitalization, (4) cause persistent or significant disability/incapacity, (5) result in congenital anomalies or birth defects, or (6) are other conditions which in the judgement of the investigators represent significant hazards*.

Based on previous experience with particular medical interventions (standard or experimental), many adverse events related to their use can be considered to be expected. For approved and marketed drugs or devices, expected adverse events are described in the approved Package Insert (Label). For investigational new drugs (INDs) or devices, information on known adverse events are described in the Investigator's Brochure required for FDA INDs. In clinical research studies, information on expected adverse events should also be summarized in the protocol and in the consent form, and may reflect clinical experience of the investigators and published reports as well as descriptions in the Investigator's Brochure and Package Insert.

PROCEDURES

Principal Investigator (PI) responsibilities:

1. The PI must propose and justify in all clinical research protocol applications a plan for collection, monitoring and analysis of adverse events. The IRB will determine whether the data and safety monitoring plan is appropriate (i.e., commensurate with the level of risk involved in the specific clinical research project).
2. Unless otherwise specified on the protocol and approved by the IRB, all **serious adverse events** must be reported by the PI verbally and in writing to the Clinical Director using the attached form. Serious adverse events, both related and unrelated to the research in the judgment of the PI, should be reported. The Clinical Director will report these events to the Director, Clinical Center, and to the IC leadership.
3. Unless otherwise specified on the protocol and approved by the IRB, the PI must report all **serious adverse events** in writing as soon as possible, but within 7 calendar days for death or life-threatening adverse events, and within 15 days for all others to the:
 - IRB (which is responsible for reporting to OSHR)
 - IND / IDE sponsor (if pertinent)
 - FDA (if NIH is the sponsor of an IND/IDE)
 - Institutional Biosafety Committee (IBC) and Office of Biotechnology Activities (OBA), NIH (if gene transfer is involved)
 - Any other oversight entities specified in the protocol or required by the IC

The Clinical Director should assure that these reporting requirements are met and receive copies of the reports.

4. The PI is responsible for summarizing **all** adverse events (*serious and non-serious, expected and unexpected*) as required by the IRB.
5. For adverse event reports presented at continuing reviews, several methodologies, including electronic databases or hard copy forms, may be utilized. The approach to be used in particular protocols should be specified by the PI in the protocol application, endorsed by study monitoring bodies, and approved by the IRB.

6. When reporting an adverse event to the IRB, the PI should address the need and method to communicate pertinent information to research subjects, the need to redesign or amend the research study plans, and whether or not a change in description of risk is warranted in the protocol and the consent form.

Institutional Review Board (IRB) responsibilities:

1. No later than at the next scheduled meeting, the IRB is responsible for the assessment of all adverse event reports in order to address both immediate issues of safety for subjects and, as necessary, any changes in protocol design and implementation needed to protect the interests of current and future research subjects.
2. When evaluating an adverse event report, the IRB must consider the following:
 - Seriousness of the event
 - Relationship of the event to the research
 - Whether the event was expected or not
 - Appropriateness of the action taken or proposed by the PI
 - Need to inform current or future subjects either by change in the protocol and informed consent document or by other written or verbal communication
3. All **unexpected serious adverse events** shall be reported in writing (including a copy of the PI adverse event report, and a summary of the IRB's discussion provided by the IRB chair) to OHSR within 14 days after the evaluation is completed by the IRB.
4. All other **unexpected adverse events** will be summarized and reported to OHSR following continuing reviews by the IRB.
5. According to the plan delineated in the approved protocol, adverse events may be analyzed by an independent study monitor or a Data and Safety Monitoring Board. The IRB and the PI shall be informed of all such adverse events and will continue to be responsible for reporting these as outlined in this document.
6. In its response to the adverse event report, the IRB is authorized to take any action necessary to safeguard research subjects, including protocol suspension or termination. IRB deliberations and actions on adverse event reports must be documented in its minutes.
7. In the case of multi-site research projects, local IRB's have the primary responsibility to evaluate and respond to serious adverse events. Serious adverse events occurring at outside sites need to be reported to OHSR only if such reports result in modification of the NIH protocol and consent documents according to the criteria above.

Appendix 1

SERIOUS ADVERSE EVENT REPORT FORM

Definition of a serious adverse event: For the purposes of this form, a serious adverse event is any untoward medical occurrence that results in death, is life-threatening, requires or prolongs hospitalization, causes persistent or significant disability/incapacity, results in congenital anomalies/birth defects, or in the opinion of the investigators represents other significant hazards or potentially serious harm to research subjects or others. A serious adverse event is considered unexpected if it is not described in the Package Insert or in the Investigator's Brochure (for FDA investigational agents), in the protocol, or in the informed consent document.

Please complete the information requested below and forward it to your Institute's IRB, with a copy to your Clinical Director, as soon as possible, but no later than seven (7) days in the case of death or life-threatening serious adverse events or within fifteen (15) days after the occurrence of all other forms of serious adverse events. In addition, continue to follow FDA and the NIH Office of Biotechnology Activities (OBA) reporting requirements if your research involves an IND / IDE or gene transfer.

1. Protocol number:
2. Protocol title:
3. Principal Investigator:
Institute:
Office:
Phone:
FAX:
E-mail:
4. Date of serious adverse event:
5. Location of serious adverse event (e.g., at NIH or elsewhere):
6. Was this an unexpected adverse event? Yes [] No []
7. Brief description of subject(s) Sex: Age:
(do not include identifiers) Diagnosis:
8. Brief description of the nature of the serious adverse event (attach description separately if more space needed):

9. Category (outcome) of the serious adverse event:

- ☐ death ☐ disability / incapacity
- ☐ life-threatening ☐ congenital anomaly / birth defect
- ☐ hospitalization-initial or prolonged ☐ required intervention to prevent permanent impairment
- ☐ other:

10. Relationship of Serious Adverse Event to research:

- ☐ 1 = Unrelated (clearly not related to the research)
- ☐ 2 = Unlikely (doubtfully related to the research)
- ☐ 3 = Possible (may be related to the research)
- ☐ 4 = Probable (likely related to the research)
- ☐ 5 = Definite (clearly related to the research)

11. Have similar adverse events occurred on this protocol? Yes ☐ No ☐

If "Yes", how many? ____ Please describe.

12. What steps do you plan to take as a result of the adverse event reported above? Provide documentation to the IRB for review and approval of any of the steps checked below.

- ☐ no action required ☐ amend protocol
- ☐ amend consent document ☐ inform current subjects
- ☐ terminate or suspend protocol
- ☐ other (describe)

Signature of Principal Investigator: _____ Date: _____

Appendix 2

Definitions

Adverse events

Any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or, if present at baseline, appears to worsen.

Serious adverse events

Any untoward medical occurrences that:

- (1) result in death,
- (2) are life threatening,
- (3) require (or prolong) hospitalization,
- (4) cause persistent or significant disability/incapacity,
- (5) result in congenital anomalies or birth defects, or
- (6) are other conditions which in the judgment of the investigators represent significant hazards.

Expected Adverse Events

For approved and marketed drugs or devices, those adverse events described in the approved Package Insert (Label). For investigational new drugs or devices, those adverse events described in the FDA Investigator's Brochure. In clinical research studies, information on expected adverse events are also summarized in the protocol and in the consent form.

Unexpected Adverse Events

Those adverse events not described in the Package Insert, Investigator's Brochure, in published medical literature, in the protocol, or in the informed consent document.

Intensity or Severity of Adverse Events

Assignment of the grade of adverse events or side-effects of interventions based on intensity of symptoms, degree of limitation of usual daily activities, or level of abnormality of objective clinical signs or laboratory parameters (schemes for assessing and monitoring adverse events can be drawn from existing models or those customized for use in particular protocols must be justified by the PI and approved by the IRB).

Relatedness of Adverse Event to an Intervention

The best estimate of the PI at the time of reporting of the causal relationship between an experimental intervention and an adverse event; the degree of certainty about causality is graded as follows:

Unrelated:

Adverse event is clearly due to extraneous causes (e.g., underlying disease, environment)

Unlikely (must have 2):

Adverse event:

- (1) does not have temporal relationship to intervention,
- (2) could readily have been produced by the subject's clinical state,
- (3) could have been due to environmental or other interventions,
- (4) does not follow known pattern of response to intervention,
- (5) does not reappear or worsen with reintroduction of intervention

Possible (must have 2):

Adverse event:

- (1) has a reasonable temporal relationship to intervention,
- (2) could not readily have been produced by the subject's clinical state,
- (3) could not readily have been due to environmental or other interventions,
- (4) follows a known pattern of response to intervention

Probable (must have 3):

Adverse event:

- (1) has a reasonable temporal relationship to intervention,
- (2) could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions,
- (3) follows a known pattern of response to intervention,
- (4) disappears or decreases with reduction in dose or cessation of intervention

Definite (must have all 4):

Adverse event:

- (1) has a reasonable temporal relationship to intervention,
- (2) could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions,
- (3) follows a known pattern of response to intervention,
- (4) disappears or decreases with reduction in dose or cessation of intervention and recurs with re-exposure